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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,899	09/28/2001	Markku Koulu	2630-111	5535

6449 7590 06/30/2004

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,899	KOULU ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,11,14 and 15* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply with sequence requirements.

DETAILED ACTION

Applicant's Response and Amendments filed 15 April 2004 have been entered.

Claims 1-3, 9-10, and 12-13 are cancelled.

Claim 8 has been amended.

Claims 14-15 have been newly added.

Claims 4-8, 11, and 14-15 are pending.

Claims 4-7 and 11 remain withdrawn from prosecution as being drawn to non-elected subject matter (See Applicant's Response to Restriction Requirement, received 4 November 2003).

Claims 8 and 14-15 are considered.

Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification discloses nucleotide and amino acid sequences in Figures 2 and 3. However, these sequences are not identified by sequence identifiers in the brief description of the figures. Moreover, the specification discloses nucleotide and amino acid sequences on page 8 of the specification, line 7.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Priority

In light of Applicant's arguments, the objections to priority are withdrawn.

Specification

In light of Applicant's amendments and arguments, the objection to the specification is withdrawn.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Pages 21-25 of the specification contain 30 references, except where such references have been submitted on Applicant's information disclosure statement or listed in a PTO-892 form.

Claim Objections

In light of Applicant's amendments and arguments, the objections to the claims are withdrawn.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 14-15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record in the Official Action of 15 January 2004 (i.e., pp. 4-6). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicant argues that the comments of the examiner concerning the written description requirements were directed to non-elected subject matter, which have been removed from the claims. As such the amendment obviates the rejection. Moreover, Applicant argues that the specification describes the use of antisense and ribozyme encoding oligonucleotides sufficiently to demonstrate that the Applicant was in possession of the presently claimed invention at the time the application was filed. (Applicants response of 15 April 2004, p. 7, first paragraph.)

Such arguments are not considered persuasive. The comments of the Examiner concern the disclosure of Applicant which could be considered for determining the required structure which would allow one of skill in the art to distinguish the various species of the genera (Official Action of 15 January 2004, p.5, second paragraph). Moreover, the Examiner also considered the required structure for antisense therapy, gene replacement, and gene switching techniques (Id., pp. 4-5, bridging paragraph). The specification does not teach the complete structure of any anti-sense nucleotide. Nor does the specification teach as to what would be the identifying characteristics of an anti-sense molecule that alters different aspects of gene expression. Lastly, with regard to the ribozymes, Applicant has not submitted any information with regard to any required structure of such ribozymes, and the specification is limited to a disclosure that "Bioengineered ribozymes are structurally different, but their specificity also relies on the recognition of the targeted mRNA sequence" (Specification, p. 8, lines 23-24). Therefore, as stated in the concluding paragraph of this rejection in the Official Action of 15 January 2004 (p. 6, first full paragraph), the information provided by Applicant is not enough convey that the Applicant is in possession of any oligonucleotide that counteracts the influence of the mutant neuropeptide Y, whether by modulating synthesis, secretion or metabolism or gene expression, at the time the application was filed.

Therefore, Claims 8 and 14-15 remain rejected for reasons of record in the Official Action of 15 January 2004.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 14-15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record in the Official Action of 15 January 2004 (i.e., pp. 6-15). The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims encompass methods of treating diabetic persons with an increased risk of developing diabetic retinopathy, due to the presence of a mutation of amino acid 7 of preproNPY from leucine to proline, by the administration of agents that counteract the influence of the mutant NPY gene. The claims are not enabled for any treatment, *in vivo*, or *ex vivo* by any agent that counteracts the mutant gene.

Response to Arguments

Applicant argues that the majority of the Examiner's analysis with regard to enablement centers on non-elected subject matter, which has been cancelled from the claims. As such, Applicants argue, the examiner has not provided any analysis specific to the elected subject matter or reasons to doubt the objective enablement of the claimed subject matter. Furthermore, Applicant asserts that the specification fully enables the claimed subject matter. (Applicants response of 15 April 2004, p. 7, fourth paragraph.)

Such arguments are not considered persuasive. First, the analysis does not center on non-elected subject matter. In fact, the analysis with regard to the prior art simply fleshes-out the field to demonstrate what is known with regard to such mutant NPY genes and what is currently

predictable in the field (Official Action of 15 January 2004, pp. 11-12). In reviewing the specific field in the state of the prior art, the Examiner concludes that in the face of a generally non-enabling nature of invention, novel gene therapy products or pharmaceuticals for *in vivo* or *ex vivo* treatment of persons suffering from any diabetes and the subject mutant preproNPY gene are not reasonably predictable to be efficacious (Id., p. 12, paragraphs 2-3). Such conclusions are inevitable when the Official Action is read in context: pages 8-10 of the Official Action of 15 January 2004 provide a detailed description of generally not-enabling nature of the invention, specifically with regard to gene therapy forms of treatment. Moreover, a synopsis of this conclusion is specifically provided on page 13 of the Official Action of 15 January 2004, where it is stated that:

> Because the art, as shown above, does not disclose any therapeutic applications for reducing any risk of diabetic retinopathy *in vivo* or *ex vivo*, and very little in the way of successful gene therapy in general, the skilled artisan at the time of invention by Applicant could not predict, in the absence of proof to the contrary, that such applications would be efficacious in reducing the risk of developing diabetic retinopathy in any diabetic person.

Furthermore, this conclusion is repeated upon an analysis of Applicant's specification (pp. 13-14, paragraph bridging) and again after an analysis of Applicant's provided examples (p. 14, second full paragraph).

Because the claims were directed in general to *any* agent, the rejection was directed to treatment with *any* agent.

Lastly, after a full examination of enablement, the Examiner continued to reject *in vivo* and *ex vivo* therapies, "whether such agent comprises gene therapy or pharmaceuticals aimed to modulate NPY expression." (p. 15, lines 1-2).

Therefore, Examiner asserts that gene therapy was given a full consideration and found not enabled. Moreover, the same rejections are applicable to the claims as presently considered for reasons of record (Official Action of 15 January 2004, pp. 6-15).

In order to help the Applicant understand this rejection and emphasize that such rejection is consonant with antisense therapy, the Examiner is providing another reference, which reference, it is maintained, is not required to be relied upon for the rejections. Lebedeva, et al. (2001) Ann. Rev. Pharm. Toxicol., 41: 403-09 provides a recent review of the use of antisense oligonucleotides to down-regulate gene expression, which although not the specific embodiment of Applicant's invention, provides support for the unpredictable nature of the art. Moreover, there is no art of record specifically addressing such antisense therapy and treating diabetic retinopathies, even outside of Applicants claimed mutant NPY genes. Lebedeva discloses many problems that must be overcome for the design and implementation of any antisense gene therapy regimen, e.g., nuclease sensitivity of the phosphodiester backbone and problems with other substitutions for the backbone, which can either prevent the drug from reaching, or acting on, its target, as well as causing unwanted and unexpected effects that may preclude the treatment which is attempted, (p. 404, first two full paragraphs, further emphasized on pp. 404-407); selection of active antisense oligonucleotide sequences is still an expensive and laborious, trial-and-error, process because with low levels of success in the art, for

unknown reasons, but may also represent toxic effects of such antisense therapy, which may preclude therapy in these cases because the cells being treated might die before therapy could be effected (p. 407, last paragraph-p. 408, first paragraph); RNase H is an enzyme of low stringency, which may cleave longer nucleotide sequences with less stringent hybridizations, leading to possible inhibition of other genes through irrelevant cleavage – which may destroy any cell being treated before any therapy could be effected (p. 408, first full paragraph-p. 409, first full paragraph); irrelevant cleavage has similarly been seen to occur in intact cells with even lower levels of complementarity (p. 409, paragraphs 3-5); problems with overly-high levels of antisense oligonucleotides *in vitro* not being reflective of *in vivo* use and a lack of a carrier in *in vitro* studies, bringing into question the specificity of the oligos (p. 411, paragraphs 2-p. 412, first paragraph); a lack of utility for antisense therapy when tested in combined regimens to treat prostate cancer (pp. 411-12); unexpected behaviors in *in vivo* studies which emphasize that the field is still immature (p. 413, second paragraph), even though some therapeutic potential for treating some cancers through Bcl-2 regulation, as a combined therapy, is promising for the future (p. 413, last paragraph-p. 414, first paragraph). All of this combined leads to the conclusion that the Artisan could not reasonably predict that enough nucleic acid would reach the target site, in large enough amounts, and have enough of an effect, without causing other unexpected effects which would preclude any therapeutic effect from occurring, and that such would occur for a long enough period of time to effect treatment.

CONCLUSION

Claims 8 and 14-15 are rejected for reasons of record in the Official Action of 15 January 2004.

It is noted that while the objection to the specification and IDS, no new rejections have been set forth. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

[X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

[ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

[ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

[ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

[ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

[ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

[ ] 7. Other: _____

Applicant Must Provide:

[X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

[X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

[X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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